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Proton pump inhibitors for chronic obstructive pulmonary disease (Protocol)

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[Intervention Protocol]

Proton pump inhibitors for chronic obstructive pulmonary disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the efficacy and safety of PPI administration for people with COPD, focusing on COPD-specific outcomes.

BACKGROUND

Description of the condition

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline defines chronic obstructive pulmonary disease (COPD) as a common, preventable and treatable disease that has a significant detrimental impact on quality of life, and poses a substantial and growing economic and social burden (GOLD 2018). COPD is one of the leading causes of global mortality and approximately three million people die due to COPD every year (WHO 2018). People with COPD have a high frequency of respiratory complications and systemic comorbidities. These comorbidities may potentiate the severity of COPD, leading to increased acute exacerbation. The latest GOLD guidelines define the COPD exacerbation as "an acute worsening of respiratory symptoms that results in additional therapy" (GOLD 2018). The healthcare costs and economic impact of COPD exacerbations are substantial, since COPD exacerbations are consistently linked to mortality, morbidity, and costly hospitalisations (Perera 2012). To address these burdens, COPD management aims to improve symptoms, prevent exacerbation and disease progression (Woodruff 2015), and management of both COPD and its comorbid conditions is important (Barnes 2013; Wedzicha 2013).

COPD is characterized by persistent respiratory symptoms and airflow limitation. GOLD specifies a post bronchodilator FEV1/FVC ratio less than 0.70 as a diagnostic criteria for COPD (GOLD 2018). Defining COPD by lung function alone may imply that COPD is a homogenous condition. However, people living with COPD have different symptoms, therapeutic response, prognosis, co-morbidities and even different causes for their condition. This heterogeneity cannot be explained by lung function alone and groups of people expressing particular characteristics can be regarded as different "phenotypes" (Han 2010). The ultimate goal

of identifying phenotypes is to aid in the determination of appropriate therapies to improve clinical outcomes.

People experiencing two or more exacerbations of COPD per year are regarded as having 'frequent exacerbations' (Hurst 2010). Patients who experienced frequent exacerbations in the past tend to exacerbate in the future and are considered to have a poor prognosis (Seemungal 1998). The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study has shown that the strongest predictor of frequent exacerbation in the future is the number of exacerbations experienced in the prior year (Hurst 2010). In addition, patients with frequent exacerbations are tend to be susceptible to viral infection (Wedzicha 2013). In other words, the management including virus infection may be effective for patients who repeatedly experience COPD exacerbations. Furthermore, some studies suggest that gastroesophageal reflux disease (GERD) is an independent predictor of frequent exacerbations (Hurst 2010; Martinez 2014; Ingebrigtsen 2015). Terada 2008 showed that the relative risk of a COPD exacerbation over two years in those with GERD is 1.93 times (95% confidence interval (CI) 1.32 to 2.84) than in those without GERD (Terada 2008).

GERD is one of the most common diagnoses that general physicians and gastroenterologists encounter in outpatients (Shaheen 2006). GERD is "defined by consensus and as such is a disease comprising symptoms, end-organ effects and complications related to the reflux of gastric contents into the oesophagus, oral cavity and/or the lung" (Katz 2013). Prevalence of GERD is rising worldwide and the disease burden is increasing (El-Serag 2014). For instance, cumulative incidence of community-acquired pneumonia (CAP) has been reported to be significantly higher in GERD patients than that in the non-GERD controls (Hsu 2017).

GERD has several causes. First, reflux occurs when the gradient of pressure between the stomach and the lower oesophageal sphincter is lost, due to low or absent lower oesophageal sphincter pressure and anatomic disruptions of the oesophagogastric junction, such as hiatal hernia (Orlando 2001). Second, oesophageal peristaltic dysfunction (a dysfunction of oesophageal contraction movement which eliminates oesophageal contents to the stomach) and prolonged oesophageal acid clearance (a dysfunction of eliminating contents in the oesophagus by the oesophageal contraction movement or secretions from the oesophagus glands, swallowed saliva) can feature in gastroesophageal reflux (Kahrilas 1988; Sugiura 2001). Especially in COPD patients, changes in lower oesophageal sphincter pressure and abnormal oesophageal peristalsis may occur due to the effect of smoking, in particular, nicotine (Pandolfino 2000). Third, some pharmacological therapies used to treat COPD, including theophylline, beta$_2$-agonists, anticholinergics, and corticosteroids, may alter oesophageal sphincter tone and respiratory mechanics, worsening the symptoms of GERD (Phulpoto 2005). In other words, some causes of GERD may be related to the cause or treatment of COPD and vice versa.

In fact, GERD is known to be a frequent comorbidity of COPD and prevalence of GERD is high in COPD patients compared with healthy controls (Mokhlesi 2001; Casanova 2004). The prevalence of GERD in people with COPD ranges from 17% to 78% (Lee 2015). The mechanism underlying GERD, which causes COPD exacerbation is thought to be related to pulmonary microaspiration of gastric acid into airways (Javorkova 2008; Lee 2015). The mechanisms can also be a risk factor for pneumonia (Terada 2008; Gaude 2009). In addition, inflammatory response by GERD, induction of airway contraction by vagal reflex, or stimulation of acid sensitive receptors in the esophageal wall may also be involved in exacerbation of COPD (Mansfield 1981; Tuchman 1984; Schan 1994). For instance, GERD is considered as one of the causes of chronic cough that is also a symptom of COPD (Irwin 2000).

Description of the intervention

Proton pump inhibitors (PPIs) are the most effective medications to reduce gastric acid secretion. Since their introduction in the late 1980s, PPIs are one of the most commonly prescribed classes of medications worldwide (Bashford 1998). Currently, seven types of PPIs (lansoprazole, omeprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole, and vonoprazan) are available, and some can be obtained over the counter at pharmacies. Vonoprazan is a novel potassium competitive PPI, which has been marketed for GERD therapy in Japan since 2015. These drugs have dramatically improved many conditions, such as peptic ulcer disease, as well as the treatment and prevention of gastroduodenal ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) (Agrawal 2000; Rostom 2002). They are also included in regimens that aim to eradicate *Helicobacter pylori* (Hu 2017). Furthermore, PPIs can prevent pulmonary microaspiration of gastric acid by reducing the production of stomach acid over the long term (Lee 2015). PPIs also make it possible to properly heal the oesophageal tissue. Hence, PPIs are the first-line drug for management of GERD (van Pinxteren 2003).

As described, GERD is an independent risk factor for frequent exacerbations of COPD (Hurst 2010). Therefore, Baumeler 2016 hypothesised that administration of PPIs for GERD might improve the symptoms and the frequency of acute exacerbations of COPD (Baumeler 2016). However, their study showed that annual COPD exacerbation rate and severity were higher in the PPI-using group than the non-treated group. Moreover, in the PPI-using group, the incidence of hypertension, heart failure, diabetes mellitus, and dementia was higher and the quality of life was lower than in the non-treated group (Baumeler 2016). Several observational studies show that there is a positive association between PPIs usage and increased risk of CAP (Laheij 2004; Gulmez 2007; Hsu 2017). Boeree 1998 also reported that their intervention study did not support the role of omeprazole to improve pulmonary symptoms and function in people with COPD (Boeree 1998). Furthermore, several meta-analysis also showed that PPI usage showed an associated with a risk of CAP (Johnstone 2010; Lambert 2015).

The following three reasons are presumed as the reason why the effect of PPI on COPD is different from Baumeler's hypothesis; (1) the effect of PPIs on bacterial infection, (2) the influence of confounding factors, and (3) other effect of PPIs (e.g. a possible protective effect against viral infections).

First, as gastric acid secretion plays a protective role against infectious agents, prolonged PPI-induced low acid status can increase the risk of bacterial overgrowth in the stomach and oesophagus (Eom 2011). This bacterial overgrowth caused by long-term PPIs may heighten the risk of bacterial aspiration (Gaude 2009). It may also be associated with an increased risk of CAP (Laheij 2004; Giuliano 2012; Lambert 2015).

Second, there are few intervention studies on this topic, and association of confounding factors may be unclear and controversial. On the one hand, Johnstone 2010 suggested that the use period of PPI may increase the risk of CAP. However, Othman 2016 suggested that this associated risk may be due to confounding. This study examined 160,000 new PPI users to investigate whether there was a change in the risk of CAP before and after the prescription of PPIs. This cohort study initially showed that the relative risk (RR) of CAP was higher (RR 1.67, 95% CI 1.55 to 1.79) in those prescribed PPI. However, after adjustment for confounding factors, the association between PPIs and CAP disappeared and PPI use was associated with a lower risk of CAP (RR 0.91, 95% CI 0.83 to 0.99).

Third, PPI may have effects other than acid suppression. Sasaki 2009 suggested a possibility of preventive effect of PPIs against viral infection, following an intervention study on how PPI administration affects exacerbation of patients with COPD. In this study, PPI (lansoprazole) administration was associated with a reduction of COPD exacerbation (Sasaki 2009). As well as bacterial infections, several viruses such as human rhinovirus (RV) have been reported to be associated with exacerbation of COPD (Hurst 2005; Falsey 2006). In previous studies, the cause of the exacerbation of COPD was thought to be mostly bacterial infection, and viral infection was considered to be the cause of about 14% to 18% of exacerbations (Buscho 1978; Smith 1980). However, in a recent report, virus detection during COPD exacerbation has been found to vary from 22% to 60% (Sethi 2008; Gunawardana 2014). Furthermore, some studies provided evidence to support a causal link between viral infection and exacerbations of COPD (Quint 2010; Beasley 2012). For instance, the phenotype that repeats exacerbation is related to virus infection (Wedzicha 2013).

As explained above, the effects of PPIs on acute exacerbation of COPD are not clear yet and controversial (Filion 2014).

Usual therapy for COPD

Updated GOLD guidelines and recently published clinical recommendations by the American Thoracic Society (ATS)/European Respiratory Society (ERS) have emphasised the benefits of smoking cessation and pharmacological therapy, including β2-agonists, anticholinergics, and corticosteroids (ATS 2017; GOLD 2018). The most appropriate pharmacological therapies should be selected for each patient according to the severity of COPD and symptoms. Asymptomatic people with mild airflow limitation can be treated with on-demand short-acting bronchodilators, such as inhalation of short-acting beta$_2$-agonists (SABA) or short-acting muscarinic antagonists (SAMA). If the symptoms do not improve, long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids are also used. If LABA or LAMA monotherapy cannot control the symptoms, administration of two or more medications may be effective (GOLD 2018). Furthermore, non-pharmacological therapies for COPD are also considered, including education and self-management, smoking cessation, nutritional guidance, pulmonary rehabilitation, immunisations, and long-term oxygen therapy, among others (GOLD 2018). To prevent acute exacerbation of COPD, it is also necessary to combine pharmacological approaches with non-pharmacological therapies.

GOLD guideline suggests that the therapeutic goal in terms of COPD exacerbation is to minimise the adverse effects on physical symptoms, respiratory function, and quality of life associated with acute exacerbations (GOLD 2018). Among several COPD clinical phenotypes, the adverse impact of frequent exacerbations is substantial. Due to this, the management strategy for acute exacerbation of COPD should be guided by phenotype (Agusti 2016).

How the intervention might work

GERD has been reported as an independent factor of COPD exacerbation (Hurst 2010). The acid suppression effect of PPI, which is the first-line drug of GERD, has the following mechanism. Gastric acid secretion is a complex process regulated by at least three types of receptors on the parietal cells (histamine, gastrin, and acetylcholine). Usually, PPIs reduce gastric acid production by irreversibly blocking the enzymes responsible for hydrogen potassium ATPase (proton pump) in parietal cells (Scott 2015; Akazawa 2016). However, unlike existing PPIs, vonoprazan reversibly blocks hydrogen potassium ATPase (proton pump) by competing with potassium ion (Hunt 2015). Vonoprazan does not require activation by acid. As a result, vonoprazan has greater and quicker acid suppression compared with existing PPIs. Thus, PPIs including vonoprazan make it possible to reduce gastric acid, and have prevent central reflex and pulmonary microaspiration of stomach acid (Lee 2015). In contrast, existing PPIs can cause gastric and oesophagus bacterial overgrowth by excessive acid suppression (Eom 2011), and may lead to COPD exacerbation (Laheij 2004; Giuliano 2012; Lambert 2015). The same safety concerns regarding vonoprazan have also been discussed (Sugano 2018). Therefore, the acid suppression effect of PPIs does not necessarily lead to reduced exacerbations, and remains controversial.

In addition to acid suppression, PPIs have been reported to have an impact on viral infection (e.g. herpes virus and rhinovirus), which

is an important causes of COPD exacerbation (Sasaki 2005; Long 2015). A randomised single-blind study showed that lansoprazole could reduce the frequency of common colds and COPD exacerbation (Sasaki 2009). Frequent COPD exacerbation suggests that exacerbators may have high sensitivity for respiratory viral infections or have poor ability to prevent viral replication (George 2014). As there are few treatment options for viral infections, this is a promising potential additional beneficial effect of PPI.

Rhinoviruses are commonly identified viruses in frequent COPD exacerbators (Hurst 2005). Rhinovirus RNA can enter across acidic endosomes of cells and it can amplify the mRNA expression of intercellular adhesion molecule-1 (ICAM-1) and cytokine (Yu 2017). ICAM-1 is the major rhinovirus infection receptor and increase viral susceptibility on respiratory epithelial cells (George 2014). Lansoprazole and omeprazole are reported to have suppressing effects on the expression of ICAM-1 mRNA (Ohara 1999; Watanabe 2001). Lansoprazole and omeprazole are thought to suppress viral infection by inhibiting vacuolar H^+-ATPase, thereby increasing endosomal pH and inhibiting the expression of ICAM-1 (Sasaki 2005). PPIs have also been suggested to have systemic anti-inflammatory effects (Becker 2006; Sasaki 2011). Viral infections induce inflammatory mediators, including various cytokines (Sethi 2008). The anti-inflammatory effect of PPIs is probably due to the effect of inhibiting the production of proinflammatory cytokines (Sasaki 2011). However, these antiviral and anti-inflammatory effects of PPIs are primarily in vitro observations. Thus, they provide insufficient evidence to conclude that PPIs have inhibitory effect on COPD exacerbations. For this reason, we should carefully consider how PPIs may affect on phenotype such as frequent exacerbations of COPD in clinical practice.

Why it is important to do this review

COPD exacerbations have a high personal and social impact (Barnes 2013; Wedzicha 2013). Therefore, prevention of COPD exacerbation is a major therapeutic target. In particular, the frequent-exacerbation phenotype of COPD is known to be associated with a history of gastroesophageal reflux or heartburn (Hurst 2010). Since PPIs have the potential to influence COPD exacerbations, and PPIs are widely available with millions of users worldwide, it is necessary to evaluate the role of PPIs in this context properly. We have identified two randomised controlled trials (RCTs) (Boeree 1998; Sasaki 2009), and some studies using other designs on this topic. However, no systematic reviews have examined RCTs of PPIs for COPD. In addition, as we mentioned previously, the effects of PPIs on acute exacerbation of COPD are still unclear and controversial (Filion 2014). Therefore, a systematic review is necessary to determine whether PPIs are useful to treat people with COPD with or without a GERD diagnosis.

OBJECTIVES

To evaluate the efficacy and safety of PPI administration for people with COPD, focusing on COPD-specific outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all RCTs in which participants are randomly assigned at the individual or cluster level. We will include studies reported as full text, those published as abstract only, and unpublished data. We will exclude cross-over trials.

Types of participants

Participant characteristics

We will include studies of adults who are over 18 years of age, of either sex, and of any ethnicity. We will include adults with a diagnosis of COPD regardless of their clinical stability; participants with stable COPD, as well as those with an acute exacerbation. We will exclude those who are prescribed PPIs within one month of study commencement the research, whether participants have GERD symptoms or not. We will also exclude studies that only include participants with asthma.

In this review we will define asthma patients as defined by the study researchers (e.g. lack of substantial smoking history and significant bronchodilator reversibility). However, we acknowledge that some studies may include participants with asthma-COPD overlap syndrome (ACOS) i.e., people with chronic asthma that causes chronic airflow limitation (Postma 2015). Such asthma patients are difficult to distinguish clearly from COPD. Thus, we will not exclude such studies, or studies that include patients who have asthma as a COPD comorbidity.

Diagnosis

We will include studies with participants diagnosed with COPD according to established criteria (e.g. the American Thoracic Society (ATS 2017), GOLD criteria (GOLD 2018)). However, we recognise that the definition of disease will change over time. If we identify older studies, we will examine the directness of the evidence in applying GRADE to the authors' diagnosis of the study. If we identify trials in which only a subset of the participants have COPD, we will include them provided disaggregated data is available or provided we can obtain it from the trial authors.

Co-morbidities

As long as the co-morbidity is not the main focus, we will include studies with participants with co-morbid chronic physical conditions (e.g. hypertension, cardiovascular disease, GERD, asthma). However, we will exclude participants with the following specific co-morbidities: bronchiectasis or genetic diseases, such as cystic fibrosis or primary ciliary dyskinesia.

Setting

All types of healthcare settings will be eligible for inclusion: primary, secondary, and tertiary care.

Types of interventions

The optimal PPI dose has not been clarified. Moreover, the standard dose of PPIs varies depending on the country and region, but is reported to be a dose within the following ranges (Iwakiri 2016; Zhang 2017).

Standard dose of PPI per day: lansoprazole, 15 mg to 30 mg; omeprazole, 10 mg to 40 mg; pantoprazole, 40 mg; rabeprazole, 10 mg to 20 mg; esomeprazole, 10 mg to 20 mg; dexlansoprazole, 30 mg to 60 mg, and vonoprazan, 10 mg to 20 mg.

Comparison: the control group will include a placebo, usual care alone, or low-dose PPI.

- Usual care plus PPI vs usual care plus placebo.
- Usual care plus PPI vs usual care alone.
- Usual care plus PPI vs usual care plus low-dose PPI.

Definition of usual care for COPD: we will classify COPD treatment as comprehensive respiratory care that supports self-management of patients and their families, drug treatment, and exacerbation measures, including lifestyle guidance on issues such as smoking cessation, vaccinations, nutritional advice, exercise therapy, and appropriate management of comorbidities. Both intervention group and comparison group can continue on their own usual care for COPD.

We will include any trials of oral PPIs administration and will exclude intravenous administration of PPIs. As it can take a few days for PPIs to exhibit a sufficient effect (Andersson 2005), and as chronic cough associated with GERD may take at least 2 to 3 months to affect the outcome (Irwin 2006), we will consider PPI therapy of at least two months' duration. We will record and compare the time of intervention and follow-up.

Types of outcome measures

Primary outcomes

- Exacerbations: exacerbation rate (participants with one or more), the time to first exacerbation after administration of PPI[1].
- Pneumonia and other serious adverse events (participants with one or more); we will report pneumonia and other serious events separately[2].

[1]We will extract the definition used for an exacerbation from each trial. Where it is not consistent, we will consider the impact on the pooled result when applying GRADE ratings (Higgins 2017).
[2]We will define serious adverse events as a serious fatal or non-fatal adverse event, which is any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongs existing hospitalisation, results in persistent or significant disability, and any important medical event that may have jeopardised the participant or requires intervention to prevent its effects (ICH 2016).

Secondary outcomes

- Quality of life (measured by a validated generic or disease-specific tool of COPD).
- Lung function: change from baseline in trough FEV1 and forced vital capacity (FVC).
- Acute respiratory infections (participants with one or more occurrences).
- Disease-specific adverse events (participants with one or more occurrence.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Group Trials Register, which is maintained by the Information Specialist for the Group. This register contains studies identified from several sources, including the following.

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org).
- Weekly searches of MEDLINE Ovid SP, 1946 to the present.
- Weekly searches of Embase Ovid SP, 1974 to the present.
- Monthly searches of PsycINFO Ovid SP, 1967 to the present.
- Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature), 1937 to the present.
- Monthly searches of AMED EBSCO (Allied and Complementary Medicine) all years to the present.
- Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Cochrane Airways Group Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of conference proceedings to be handsearched, are shown in Appendix

1. See Appendix 2 for search terms we will use to identify studies for this review.

We will search the following trials registries.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will search the Cochrane Airways Trials Register and additional sources from inception to the present, with no restriction on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for study information.

We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and will report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (SK and YN) will independently screen the titles and abstracts of the search results and code them as either 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (SK and YN) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (TT). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (SK) will extract the following study characteristics from the included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
- Participants: number (N), mean age, age range, gender, severity of condition, diagnostic criteria, follow-up duration, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, excluded medications, and dosage of the intervention.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for studies and notable conflicts of interest of trial authors and other information if necessary.

Two review authors (SK and YN) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if the study authors did not report outcome data in a usable way. We will resolve disagreements by consensus or by involving a third review author (TT). One review author (SK) will transfer data into the Review Manager 5 (RevMan 5) file (RevMan 2014). We will check that the data are entered correctly by undertaking double data entry. A second review author (YN) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SK and YN) will independently assess the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreements by discussion or by involving a third review author (TT). We will assess the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We will judge each potential source of bias as either 'high', 'low', or 'unclear' and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table for each study. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trial author, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as relative risk (RR) values and continuous data as mean difference (MD) or standardised mean difference (SMD) values. If we combine data from rating scales in a meta-analysis, we will ensure we enter them with a consistent direction of effect (e.g. lower scores always indicate improvement).
We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.
We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).
Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.
If a study reports outcomes at multiple time points, we will use the last time point measured.
We will conduct an 'as reported' and intention to treat (ITT) analysis of the primary outcome. We will assess the secondary outcomes using an 'as reported' analysis.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of patients admitted to hospital, rather than number of admissions per patient). However, if data were to permit the calculation of rate ratios (e.g. exacerbation rates), we will analyse them on this basis, since this allows the inclusion of more than one event in a participant over the time of the trial. We will meta-analyse data from cluster-RCTs only if available data have been adjusted (or can be adjusted) to account for clustering.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only).
If we cannot reach the study authors, we intend to deal with missing participants using an ITT analysis, assuming that missing participants have failed treatment. In the case of dichotomous data when treatment response is compared, we will include the total number of participants randomised to each comparison group (as the denominator). In the analyses of treatment response, we will only include data from trials that report a group size prior to drop outs. For continuous outcome measures, we will include summary statistics derived from mixed-effect models, the last observation carried forward, and observed cases' summary statistics. This is dictated by the notion that mixed-effect models are considered less biased than the analyses of the last observation carried forward.
We will investigate the impact of imputation on meta-analysis by performing sensitivity analyses and will report per outcome. Where missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis (i.e. if treatments, participants, and the underlying clinical question are similar enough among trials). We will explore statistical diversity by estimates of treatment effect through Forest plots created in RevMan 5 (RevMan 2014). Heterogeneity might not be important when the I^2 statistic value is between 0% and 40%; there may be moderate heterogeneity when the I^2 statistic value is between 30% and 60%; substantial heterogeneity when I^2 is between 50% and 90%; and considerable heterogeneity when the I^2 is greater than 75% (Higgins 2017). If we identify substantial heterogeneity we will report it and will explore the possible causes by prespecified subgroup analysis. We will consider a Chi^2 test P value of less than 0.10 indicative of statistical heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create a funnel plot of effect estimates against their standard errors to explore possible small study and publication biases. We will consider possible explanations if we find asymmetry of the funnel plot.

Data synthesis

When participants, interventions, comparisons, and outcomes are sufficiently similar to make clinical sense, we will combine the results from similar studies by undertaking a meta-analysis using RevMan 5 (RevMan 2014). We will use a random-effects model by default.
If substantial or considerable unexplained heterogeneity (> 60%) is present, we will not perform meta-analysis (see Assessment of heterogeneity).

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes.

- Primary outcomes: exacerbations, and pneumonia and other serious adverse events.
- Secondary outcomes: quality of life, lung function, acute respiratory infections, disease-specific adverse events.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017; Schünemann 2017), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of the evidence using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We will present the primary outcomes in subgroup analyses. We plan to carry out the following subgroup analyses if data are available.

- Baseline severity of COPD using GOLD spirometric assessment (GOLD 2018). GOLD 1: mild (FEV1 $\geq$ 80% predicted), GOLD 2: moderate (50% $\leq$ FEV1 < 80% predicted), GOLD 3: severe (30% $\leq$ FEV1 < 50% predicted), GOLD 4: very severe (FEV1 < 30% predicted).
- PPI subtype (lansoprazole or omeprazole, other PPIs). Lansoprazole and omeprazole have been reported to inhibit cytokine production of proinflammatory cytokines, and are expected to reduce the frequency of catching colds (Sasaki 2009).
- GERD symptoms at baseline: dichotomised as either yes or no according to inclusion criteria.
- Trial funding sources (financial sponsorship from the pharmaceutical industry selling PPIs, non-industry-sponsored studies).

We will use the following outcomes in subgroup analyses.

- Exacerbations.
- Pneumonia and other serious adverse events.
- Quality of life.
- Acute respiratory infections.

We will use the formal test for subgroup interactions in RevMan 5 (RevMan 2014).

Sensitivity analysis

We plan to undertake sensitivity analyses by removing the following studies from the primary outcome analyses to assess the robustness of our conclusions.

- We will exclude studies with high risk of bias based on the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017) (i.e. studies that lack at least two of the following domains: allocation concealment, blinding of outcome assessors, or complete outcome data).

Sensitivity analysis will be limited to the primary outcomes. We will compare the results from a fixed-effect model with the random-effects model.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE (Ovid) search strategy used to identify studies for the Cochrane Airways Trials Register

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify studies in other electronic databases.

Appendix 2. Cochrane Airways Trials Register (via the Cochrane Register of Studies (CRS)) search strategy

#1	MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2	MeSH DESCRIPTOR Bronchitis, Chronic
#3	(obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4	COPD:MISC1
#5	(COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	MESH DESCRIPTOR Proton Pump Inhibitors EXPLODE ALL
#8	Proton Pump Inhibitor* or "Proton-Pump Inhibitor*" or PPI or PPIs
#9	lansoprazole

(*Continued*)

#10	omeprazole
#11	pantoprazole
#12	rabeprazole
#13	esomeprazole
#14	dexlansoprazole
#15	vonoprazan
#16	MESH DESCRIPTOR Gastroesophageal Reflux EXPLODE ALL
#17	MESH DESCRIPTOR Laryngopharyngeal Reflux EXPLODE ALL
#18	((gastroesophageal or gastro-esophageal or gastro-oesophageal or gastrooesophageal) NEAR3 reflux)
#19	GERD or GORD
#20	acid NEAR2 reflux
#21	heartburn or pyrosis
#22	{OR #7-#21}
#23	#22 AND #6

CONTRIBUTIONS OF AUTHORS

Shino Kikuchi (SK) and Yoko Naoki (YN) wrote the first draft of the protocol. Tomoko Tajiri (TT) and Norio Watanabe (NW) commented and contributed to the protocol and approved it before its publication.

DECLARATIONS OF INTEREST

SK has no known conflicts of interest.

YN has no known conflicts of interest.

TT has no known conflicts of interest.

NW has no known conflicts of interest.

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